II. PEPTIDERGIC CONTROL OF CIRCADIAN TIMING: ROLE OF NEUROPEPTIDE Y (NPY)

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Circadian clocks generate 24-hr rhythms which are synchronized with the 24-hr day-night cycle. The suprachiasmatic nucleus (SCN) functions as a circadian clock in mammals, and several afferent projections of this nucleus appear to communicate the photic information necessary for synchronizing rhythms with the day-night cycle. One of these afferent pathways is the geniculohypothalamic tract (GHT) which is a secondary photic projection from the intergeniculate leaflet of the thalamus to the SCN. The principal neurotransmitter in the GHT appears to be NPY. Previously, we have demonstrated that microinjection of NPY into the SCN region phase shifts circadian activity rhythms in a manner which mimics the phase shifts produced by pulses of darkness and several other non-photic stimuli (e.g. locomotor activity). The following experiments investigated whether NPY acts directly on the clock within the SCN to produce phase shifts or whether NPY acts indirectly through other neurochemical signals to produce phase shifts. One neurochemical signal through which NPY might indirectly influence the clock in the SCN is GABA. GABA has been found in all or nearly all SCN neurons. To determine if GABA can influence the phase shifting effects of NPY, the $GABA_A$ antagonist, bicuculline, was injected into the SCN region with NPY. Bicuculline significantly reduced the phase advancing effects of NPY when compared to NPY injected with vehicle control, while bicuculline injected alone had little or no phase shifting effect. To further investigate whether the phase shifting effects of NPY are the result of a direct action on the clock mechanism, NPY was microinjected with tetrodotoxin (TTX) which should block sodium-dependent synaptic activity. TTX significantly reduced the phase advancing effects of NPY while producing no phase shifts when administered alone. These data support the hypothesis that NPY phase advances circadian rhythms by indirectly influencing the clock within the SCN, perhaps through a $GABA_A$-dependent mechanism.

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